IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Kemmerer, Elizabeth
Avi Ahskenazi, *et al.*	)	Art Unit: 1646
Application Serial No. 09/904,766	)	Confirmation No: 4054
Filed: July 12, 2001	)	Attorney's Docket No. 39780-1618 P2C33
For: **PRO269 POLYPEPTIDES**	)	**Customer No. 35489**

EXPRESS MAIL LABEL NO. EV 765 984 886 US
DATE MAILED: AUGUST 29, 2007

ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES
APPELLANTS' BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 32613-1450

Dear Sir:

This Appeal Brief, filed in connection with the above captioned patent application, is responsive to the Final Office Action mailed on November 1, 2006. A Notice of Appeal was filed herein on May 1, 2007. A request for a two-month extension of time is requested herewith. Appellants hereby appeal to the Board of Patent Appeals and Interferences from the final rejection in this case.

The following constitutes the Appellants' Brief on Appeal.

I. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the parent application, U.S. Patent Application Serial No. 09/665,350 recorded July 9, 2001, at Reel 011964 and Frame 0181. The present application is a continuation of U.S. Serial No. 09/665,350.

II. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to a polypeptide referred to herein as "PRO269." There exist two related patent applications, (1) U.S. Patent Application Serial No. 09/907,841, now Patent No. 7, 033, 825, issued 04-25-2006 (containing claims directed to nucleic acids encoding PRO269 polypeptides), and (2) U.S. Patent Application Serial No. 09/902,713, filed November 10, 2001 (containing claims directed to PRO269 antibodies). Related U.S. Patent Application Serial No. 09/902,713 application is also under final rejection by the same Examiner, and based upon the same outstanding rejections, is being appealed independently and concurrently herewith. Although there exist several applications directed to the "gene amplification" utility, in general, under Appeal, none of these are related to PRO269 molecules or antibodies binding to it.

III. STATUS OF CLAIMS

Claims 44-46 and 49-52 are in this application.

Claims 1-38 and 47-48 have been canceled.

Claims 44-46 and 49-52 stand rejected and Appellants appeal the rejection of these claims.

IV. STATUS OF AMENDMENTS

A summary of the prosecution history for this case is as follows:

Previously, in response to a Final Office Action mailed on January 13, 2005, a Notice of Appeal was filed on June 13, 2005 and an Appeal Brief was filed on September 13, 2005. An Examiner's Answer was mailed on November 15, 2005 which cited new references; hence, a Reply Brief was filed January 17, 2006 with a Petition for Designation of New Grounds of Rejection and with a request to withdraw finality of the rejection under 37 C.F.R. §1.181. The

Decision on the Petition granting the Appellants' request to have the finality withdrawn was mailed on January 30, 2006. Therefore, a Supplemental Response with additional references and affidavits supporting Appellants' arguments was filed March 30, 2006. In response to a Final Office Action dated April 21, 2006, an RCE response was filed on August 22, 2006 with further references and affidavits supporting Appellants' arguments. A Final Office Action was mailed on November 1, 2006, and a Response and a Notice of Appeal were filed May 1, 2007. An Advisory Action was mailed May 30, 2007.

No claim amendments have been submitted after the Response mailed May 1, 2007.

A copy of the rejected claims in the present Appeal is provided in Section VIII.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the present application is related to an isolated polypeptide comprising (a) the amino acid sequence of the polypeptide of SEQ ID NO:96; (b) the amino acid sequence of the polypeptide-of SEQ ID NO:96, lacking its associated signal peptide; (c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO:96; or (d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209397 (Claims 44-46, 49 and 52). The claims are further directed to a chimeric polypeptide comprising a polypeptide according to Claim 44 fused to a heterologous polypeptide (Claim 50). The claims are further directed to a chimeric polypeptide according to Claim 50 wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin (Claim 51).

The full-length PRO269 polypeptide having the amino acid sequence of SEQ ID NO:96 is described in the specification at, for example, page 12, line 30 to page 13, line 1, page 40, lines 1-11, page 103, lines 4-12, in Figure 36 and in SEQ ID NO:96. PRO269 is described as a novel polypeptide having a signal peptide sequence and a transmembrane domain (see, for example, Example 15 and Figure 36). Example 92, in the specification at page 222, line 26, to page 235, line 3, sets forth a 'Gene Amplification assay' which shows that the PRO269 gene is amplified, approximately **2-3.5 fold amplification in 8 primary lung tumors and tumor cell lines**. (see page Table 9). The profiles of various primary lung tumors used for screening the PRO polypeptide compounds of the invention in the gene amplification assay are summarized on Table 8, page 227 of the specification.

The cDNA nucleic acid encoding PRO269 is described in the specification at, for example, Example 15, in Figure 35 and in SEQ ID NO:95. Page 60, lines 18-22 of the specification provides the description for Figures 35 and 36. The preparation of chimeric PRO polypeptides, including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin, is set forth in the specification at page 116, lines 12-35. Examples 53-56 describe the expression of PRO polypeptides in various host cells, including *E. coli*, mammalian cells, yeast and Baculovirus-infected insect cells.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether Claims 44-46 and 49-52 satisfy the utility/ enablement requirement under 35 U.S.C. §§101/112, first paragraph.

VII. ARGUMENTS

Summary of the Arguments:

Issue 1: Utility/ Enablement

As a preliminary matter, Appellants note that, in the recent Advisory Action, the Examiner has withdrawn rejections based on references Chen *et al.*, Hu *et al.*, LaBaer *et al.*, Haynes *et al.*, Gygi *et al.*, Lian *et al.*, Fessler *et al.*, Greenbaum *et al.*, Nagaraja *et al.*, Waghray *et al.*, Sagynaliev *et al.*, Lilley *et al.*, King *et al.*, Bork *et al.*, Madoz-Gurpide *et al.*, cited previously against the Appellant (Advisory Action mailed May 30, 2007, page 2, paragraph 1). The Examiner adds that "references cited by the Applicant pertaining to the mRNA/polypeptide correlation issue will no longer be addressed: Futcher *et al.*, Alberts and Lewin, Zhigang *et al.*, Meric *et al.*, Wang *et al.*, Munaut *et al.*, Celis *et al.*, Maruyama *et al.*, Rudlowski *et al.*" (Advisory Action mailed May 30, 2007, page 2, paragraph 1). Accordingly, these references are no longer discussed in this Appeal Brief. The Examiner adds that "(t)he basis of the maintained rejections is solely that gene amplification levels are not predictive of mRNA or polypeptide levels" (Advisory Action mailed May 30, 2007, page 2, paragraph 1).

The gene amplification assay measures the level at which a certain gene (i.e. DNA) is amplified in the genome, whereas the microarray assay measures the level of expression of a mRNA encoding for a certain polypeptide in a sample. Appellants would like to bring to the

Examiner's attention a recent decision in a microarray case (which is not the same as the gene amplification assay but whose results are nevertheless applicable here), by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9). Appellants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the PRO269 polypeptide to refute Applicant's assertion of a correlation between DNA levels, mRNA levels and protein expression.

Appellants rely upon the gene amplification data of the PRO269 gene for patentable utility of the PRO269 polypeptides. This data is clearly disclosed in the instant specification in Example 92 which discloses that the gene encoding PRO269 showed significant amplification, ranging from **2-3.5 fold amplification in 8 primary lung tumors and tumor cell lines**. Appellants have submitted, in their Response filed February 21, 2003, a Declaration by Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of lung cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

Appellants have also submitted, in their Responses filed May 21, 2004, November 3, 2004 and March 30, 2006, ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For instance, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* collectively teach that in general, gene amplification increases mRNA expression. Second, the Declarations of Dr. Paul Polakis: (Polakis I and II), shows that, in general, there is a correlation between mRNA levels and polypeptide levels. Third, Appellants further submit that even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Appellants expressly do not concede to), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Appellants submit that, as evidenced by the

Ashkenazi Declaration and the teachings of Hanna and Mornin (both made of record in Appellants' Response filed May 21, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu.

Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (*i.e.,* that it is more likely than not informative of the protein level). Therefore, as a general rule, one skilled in the art would find it more likely than not that PRO269 and antibodies binding to the PRO269 polypeptides are useful as a diagnostic tools for detecting lung tumors.

The Examiner further cites the Sen reference indicating that the gene amplification results did not consider aneuploidy as a possibility.

Appellants submit that even if the amplification of the PRO269 gene were due to aneuploidy (which Appellants expressly do not concede with), the art exemplified by the Sen *et al.* reference still supports the Appellants' position because it still provides utility for the PRO269 gene, at least as a marker for cancer or precancerous cells or damaged tissue. Accordingly, the PRO269 gene finds utility as a diagnostic for cancer or for individuals at risk for developing lung cancer.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is generally a positive correlation between DNA, mRNA, and polypeptide levels, in general, in the majority of amplified genes, as exemplified by the teachings of Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* the Polakis Declaration, the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. The widespread, art accepted use of information obtained from array chips for detecting diagnostic markers lend further support that in general, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO269 gene, that the PRO269 polypeptide is concomitantly overexpressed and has utility in the diagnosis of lung cancer or for individuals at risk for developing lung cancer.

Accordingly, Appellants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed PRO269 polypeptides. Accordingly, one of ordinary skill in the art would also understand how to make and use the recited polypeptides for the diagnosis of lung cancer without any undue experimentation.

These arguments are all discussed in further detail below under the appropriate headings.

Response to Rejections

ISSUE 1. Claims 44-46 and 49-52 are Supported by a Credible, Specific and Substantial Asserted Utility, and Thus Meet the Utility Requirement of 35 U.S.C. §101 and the "How to Use Prong" of the Enablement Requirement of 35 U.S.C. §112, First Paragraph

The sole basis for the Examiner's rejection of Claims 39-43 under these sections is that the data presented in Example 92 of the present specification is allegedly insufficient under applicable legal standards to establish a patentable utility under 35 U.S.C. §101 for the presently claimed subject matter, and further, since a patentable utility has not been established, one would not know how to use the claimed invention.

Appellants strongly disagree and respectfully traverse the rejection.

A. The Legal Standard For Utility Under 35 U.S.C. §101

According to 35 U.S.C. §101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added).

In interpreting the utility requirement, in *Brenner v. Manson,*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent Applicant disclose a "substantial utility" for his or her invention, *i.e.,* a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but

---

[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler,*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The Court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka,*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, *i.e.,* there is a reasonable correlation there between."[7] The Court perceived, "No insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."[8]

The case law has also clearly established that Appellants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that Appellants' claims of usefulness are not believable on their face.[10] In

---

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

general, an Appellant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11, 12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines"),[15] which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention

---

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) *cert. denied,* 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial utility.'"[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

B. Proper Application of the Legal Standard

Appellants submit that the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant.

Appellants respectfully submit that the data presented in Example 92 starting on page 539 of the specification and the cumulative evidence of record support a "specific, substantial and credible" asserted utility for the presently claimed invention.

Patentable utility for the PRO269 polypeptides is based upon the gene amplification data for the gene encoding the PRO269 polypeptide of SEQ ID NO: 96. Example 92 describes the results obtained using a very well-known and routinely employed polymerase chain reaction (PCR)-based assay, the TaqMan™ PCR assay, also referred to herein as the gene amplification assay. This assay allows one to quantitatively measure the level of gene amplification in a given sample, say, a tumor extract, or a cell line. It was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Appellants isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9, including primary lung cancers of the type and stage indicated in Table 8 of the

---

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II(B)(1).

specification. The tumor samples were tested in triplicates with Taqman™ primers and with internal controls, beta-actin and GADPH in order to quantitatively compare DNA levels between samples. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control and also, no-template controls (pages 222-234). The results of TaqMan™ PCR are reported in ΔCt units, as explained in the passage on pages 222-223. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on. Using this PCR-based assay, Appellants showed that the gene encoding for PRO269 was amplified, that is, it showed approximately 1.04-1.60 ΔCt units which corresponds to **2.00-3.5-fold** amplification in eight primary lung tumors or cell lines.

Appellants submitted a Declaration by Dr. Audrey Goddard which provides a statement by an expert in the relevant art that "fold amplification" values of at least 2-fold are considered significant in the TaqMan™ PCR gene amplification assay. Appellants particularly draw the Board's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Accordingly, the **2-3.5 fold amplification in 8 primary lung tumors and tumor cell lines** would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration.

Further, as discussed in detail below, Appellants have provided ample evidence in the form of articles from the art, like Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and over a 100 references (see Evidence List submitted on August 22, 2006) and Declarations by experts in the field of oncology and gene expression, i.e.: the Declarations by Dr. Paul Polakis (I and II) and by

Dr. Avi Ashkenazi , to show that, in general, if a gene is amplified in cancer, it is "more likely than not" that the encoded protein will also be expressed at an elevated level.

C. A *prima facie* case of lack of utility has not been established

As discussed above, the increase in DNA copy number for the PRO269 gene is significant. Further, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.

Accordingly, it is not a legal requirement to establish a necessary correlation between an increase in the copy number of the DNA and protein expression levels that would correlate to the disease state or that it is imperative to find evidence that DNA amplification is "necessarily" or "always" associated with overexpression of the gene product. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant.

Previously, the Examiner has indicated based on references Pennica *et al.*, Konopka *et al.* to show that gene amplification data cannot reliably predict protein levels. The Examiner has withdrawn rejections based on references Hu *et al.*, Haynes *et al.*, Gygi *et al.*, Lian *et al.*, Fessler *et al.* and Greenbaum *et al.* Accordingly, these references are no longer discussed in this Appeal Brief. Appellants have argued the references in great detail throughout prosecution, and these arguments are incorporated by reference herein for brevity. Appellants summarize the rejections and the arguments submitted below.

The teachings of Pennica *et al.* are specific to *WISP* genes, a specific class of closely related molecules. Pennica *et al.* showed that there was good correlation between DNA and mRNA expression levels for the *WISP-1* gene but not for *WISP-2 and WISP-3* genes. WISPs 1-3 have no structural relationship to the PRO269 polypeptides of the present application. The apparent finding that for two out of three specific molecules, that are related to each other but have no relationship to PRO269, there was no correlation between gene amplification and the level of mRNA/protein expression does not establish, in general, that it is more likely than not

that such correlation does not exist, and has no bearing whatsoever on determining the question whether such correlation is likely to exist between PRO269 gene amplification and mRNA/protein expression levels. As discussed above, the standard is not absolute certainty. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression for genes in general, or PRO269 or related molecules in particular.

Similarly, in Konopka *et al.*, the Examiner has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that "[p]rotein expression is not related to amplification of the ***abl*** gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph^1 template." (See Konopka *et al* ., Abstract, emphasis added). The paper does not teach anything whatsoever about the correlation of protein expression and gene amplification in general, and provides no basis for the generalization that apparently underlies the present rejection. The statement of Konopka *et al.* that "[p]rotein expression is not related to amplification of the *abl* gene . . . " is not sufficient to establish a *prima facie* case of lack of utility. Therefore, the combined teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels. In addition, the *abl* gene has no structural relationship to the PRO269 gene of the present application and thus Konopka *et al.* provides no information of specific relevance to the question whether for PRO269 there is a reasonable expectation that correlation between gene amplification and mRNA/protein expression levels is likely to exist.

Since *accurate prediction* is not the standard, a *prima facie* case of lack of utility has not been met based on the cited references Pennica *et al.*, Konopka *et al.* Appellants respectfully submit that, contrary to the Examiner's assertion, none of the cited reference conclusively establish a *prima facie* case for lack of utility for the PRO269 molecule.

Godbout *et al.* and Bea *et al.*

The Examiner asserts that Godbout speak to general lack of correlation between gene amplification and mRNA/ protein overexpression. The Examiner adds that "a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified" and further that "it is generally accepted that co-amplified

genes are not over-expressed unless they provide a selective growth advantage to the cell". The Examiner adds that "there is no evidence that PRO269 confers any growth advantage to a cell, and thus it cannot be presumed that the protein is overexpressed because the gene is amplified" (Advisory Action of May 30, 2007).

Appellants respectfully disagree with the Examiner's conclusions. First of all, as discussed in the RCE response of August 22, 2006, the Godbout *et al.* and Bea *et al.* references were presented to show good correlation between protein levels based upon genomic DNA amplification..

Regarding Godbout *et al.*, Appellants respectfully submit that the passage cited by the Examiner regarding selective advantage is based upon two references from 1987 and 1992. In contrast, Appellants have made of record three more recent references, published in 2002, by Ornoft *et al.*, Hyman *et al.*, and Pollack *et al*, (made of record in Appellants' Response filed November 3, 2004), which collectively teach that in general, gene amplification increases mRNA expression. Appellants submit that these more recent references must be acknowledged as more accurately reflecting the state of the art regarding the correlation between gene amplification and transcript expression, than the references referred to in Godbout *et al.*

Appellants also respectfully submit that Bea *et al.* investigated gene amplification, mRNA expression, and protein expression of the putative oncogene BMI-1 in human lymphoma samples, which supports Appellants' assertion that gene amplification is correlated with both increased mRNA and protein expression.

Orntoft *et al.*

The Examiner asserts that "Orntoft concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40)" and asserts that such an analysis was not done for PRO269.

While technical considerations prevented Orntoft *et al.* from evaluating a larger number of proteins, the ones they did look at showed a clear correlation between mRNA and protein expression levels. For instance, Orntoft found that "[i]n general **there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations**. Only one gene [of the 40 examined] showed disagreement between transcript alteration and protein alteration." (Page 42,

col. 2; Emphasis added). Clearly, a correlation in 39 of 40 genes examined supports the Appellants assertion that changes in mRNA level generally lead to corresponding changes in protein level.

As discussed before, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not whether a necessary or even "strong" correlation between an increase in mRNA and protein expression levels exists, but whether it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. In particular, among the 26 tested proteins of the TCC pair 733 and 335 referenced by the Examiner, about 19 proteins show a positive correlation between the mRNA and the protein. That is, Ornoft teaches that there is about a 73% probability (more than 50% and this is "more likely than not") that a protein expression level correlates with a mRNA expression level. Therefore, the teachings of Ornoft clearly support Appellants position.

Wildsmith *et al.*

Although the Examiner has withdrawn the rejections based on Lilley *et al.*, King *et al.*, Nagaraja *et al.*, Waghray *et al.*, Sagynaliev *et al.*, in the Advisory Action of May 30, 2007, the Examiner did withdraw reference Wildsmith *et al.* (cited in the Final Office action of November 1, 2006). Therefore, Appellants discuss this reference below.

Like Lilley *et al.*, King *et al.*, Nagaraja *et al.*, Waghray *et al.*, Sagynaliev *et al.*, Wildsmith *et al.* refers to the microarray assay. Appellants repeat that it is not a legal requirement for utility, to establish a necessary correlation between an increase in the mRNA level and protein expression levels, or to show that changes in transcript level should always result in corresponding changes in protein amount or activity. Accordingly, the question is not whether a correlation between an increase in mRNA and protein expression levels always exists, rather if it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Wildsmith never indicated that it is more likely than not that a general correlation between the mRNA and protein levels for a gene does not exist. Therefore, this paper is not sufficient to establish a *prima facie* showing of lack of utility. In fact, the Wildsmith paper discusses examples of a number of successes of microarray

applications in the detection of human diseases (see Page 284). For instance, the author has pointed out that "one area of rapid progress using microarray technology is the increased understanding of cancer. Molecular pathologies are subgrouping cancers of tissues such as blood, skin, and breast, based on differential gene expression patterns. For example, within a small group of breast cancer tissue samples, Perou *et al.* distinguished two broad subgroups representing those expressing or alternatively lacking expression of the oestrogen receptor- ÿ-gene. The work was not conclusive, but never has progress in this field been so rapid when compared with the previous methods of gene amplification. Another example of the impact of this technology is in the identification of two biomarkers for prostate cancer, namely hepsin and PIM1 (Dhanasekaran *et al.*, 2001). Microarray technology has also accelerated the understanding of the molecular events surrounding pulmonary fibrosis. Specially, two distinct clusters of genes associated with imflammation and fibrosis have been identified in a disease where, for years, the pathogenesis and treatment have remained unknown (Katsuma *et al.*, 2001)."

Therefore, the reference Wildsmith *et al.*, like Lilley and King *et al.* references, show that the art indicates that, generally, if a mRNA is overexpressed in cancer, it is more likely than not that the encoded protein will also be expressed at an elevated level.

Li *et al.*

The Examiner maintains the rejection based on Li *et al.* as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." (Advisory Action of May 30, 2007).

Appellants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma" (page 2629, col. 1). For instance, as explained in the Supplemental Information accompanying the Li article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. In the case of PRO269, as discussed in previously filed responses and in the Goddard Declaration (of record), an appropriate threshold for considering gene amplification to be significant is a copy number of

at least 2.0 (which is a higher threshold). The PRO269 gene showed significant amplification of **2-3.5 fold amplification in 8 primary lung tumors and tumor cell lines**, and thus fully meets this standard. It is not surprising that, in the Li *et al.* reference, by using a lower threshold of 1.4 for considering gene amplification, a higher number of genes not showing corresponding increases in mRNA expression were found. Nevertheless, the results of Li *et al.* do not conclusively disprove that a gene with a substantially higher level of gene amplification, such as PRO269, would be expected to show a corresponding increase in transcript expression.

Therefore, the Patent Office has failed to meet its initial burden of proof that Appellants' claims of utility are not substantial or credible. The arguments presented by the Examiner based on references Pennica *et al.*, Konopka *et al.*, Wildsmith *et al.* and Li *et al.*, do not provide sufficient reasons to doubt the statements by Appellants that PRO269 has utility as a diagnostic marker for lung cancer. Appellants once again remind the Examiner that only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant. Based on the above discussions, such a showing has not been made. Accordingly, the instant rejection should be withdrawn for the Examiner's lack of establishment of a *prima facie* showing.

Sen *et al.*

The Examiner argues, based on the Sen reference, that "(t)he art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy before the epithelial cells turn cancerous...Sen teach that damaged, precancerous lung epithelium is often aneuploid."

Appellants submit that, even if the amplification of the PRO269 gene were due to chromosomal aneuploidy (which Appellants expressly do not concede to), the art exemplified by the Sen *et al.* reference still supports the Appellants' position for utility, because there is utility for an aneuploid gene at least as a marker for cancer or precancerous cells or damaged tissue. As is well-known in the art, studies on premalignant lung lesions suggest that epithelial tumors develop through a multistep process driven by genetic instability. In other words, cancer is a manifestation of a multistep tumorigenesis process. Therefore, contrary to the Examiner's interpretation, the Sen reference strongly supports the Appellants position that there is utility in

identifying genetic biomarkers in epithelial tissues at cancer risk. Therefore, even if Appellants were to show that the observed PRO269 gene amplification were due to chromosomal aneuploidy (which Appellants do not contend to), identification of such a genetic biomarkers is a very important and useful step, in identifying individuals at significantly increased cancer risk. In fact, one skilled in the art would find it entirely reasonable that early detection of lung cancer would provide vital, advance information regarding risk assessment, prognosis and therapy for lung cancer. Accordingly, the PRO269 polypeptides find utility at least as diagnostic markers for individuals at risk of developing lung cancer, for the reasons discussed above. Thus, a *prima facie* case for lack of utility has not been made based on the Sen reference.

In summary, Appellants maintain that even though there are certain instances where a correlation, between DNA/mRNA and protein levels do not exist, in most cases, there is generally good correlation between them, and this was collectively demonstrated in the more than 100 references submitted by the Appellants in the IDS filed August 22, 2006.

D. The Gene Amplification Data Establishes Credible, Substantial and Specific Patentable Utility for the PRO269 Polypeptide and its Antibodies

On the other hand, as discussed throughout prosecution, Appellants submit that Example 92 of the specification further discloses that, "(a)mplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as lung, colon, breast and other cancers and diagnostic determination of the presence of those cancers" (Emphasis added). Appellants have also submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is "more likely than not" that the encoded protein will also be expressed at an elevated level.

Besides the reference, the Declaration by Dr. Paul Polakis (Polakis I - made of record in Appellants' Response filed November 3, 2004), principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, explains that in the course of Dr. Polakis' research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Appellants submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels. The second Declaration by Dr. Polakis (Polakis II) presented evidentiary

data in Exhibit B. Exhibit B of the Declaration identified 28 gene transcripts out of 31 gene transcripts (*i.e.*, greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions regarding protein data. Appellants further emphasize that the opinions expressed in the Polakis Declaration, including in the above quoted statement, are all based on factual findings. For instance, antibodies binding to about 30 of these tumor antigens were prepared and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Therefore, Dr. Polakis' research, which is referenced in his Declaration, shows that, in general, there is a correlation between increased mRNA and polypeptide levels. Hence, one of skill in the art would reasonably expect that, based on the gene amplification data of the PRO269 gene, the PRO269 polypeptide is concomitantly overexpressed in lung tumors studied as well.

Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip® arrays in 2004. Clearly, the research community believe that the information obtained from these chips is useful (*i.e.*, that it is more likely than not that the results are informative of protein levels).

Thus, based on the asserted utility for PRO269 in the diagnosis of lung tumors, the reduction to practice of the instantly claimed protein sequence of SEQ ID NO: 96 in the present application (see page 12, line 30 to page 13, line 1; page 40, lines 1-11, page 103, lines 4-12), the disclosure of the step-by-step protocols for making chimeric PRO polypeptides, including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin in the specification (at page 116, lines 12 to 359), the disclosure of a step-by-step protocol for making and expressing PRO269 in appropriate host cells (in Examples 53-56), the step-by-step

protocol for the preparation, isolation and detection of monoclonal, polyclonal and other types of antibodies against the PRO269 protein in the specification (in Examples 57-59) and the disclosure of the gene amplification assay in Example 92, the skilled artisan would know exactly how to make and use the claimed polypeptide and its antibodies for the diagnosis of lung cancers. Appellants submit that based on the detailed information presented in the specification and the advanced state of the art in oncology, the skilled artisan would have found such testing routine and not 'undue.'

Therefore, Appellants respectfully request reconsideration and reversal of this outstanding rejections under 35 U.S.C. §101 and §112, First Paragraph to Claims 44-46 and 49-52.

CONCLUSION

For the reasons given above, Appellants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed polypeptide and its antibodies. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of Claims 44-46 and 49-52.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-1618P2C33**).

Respectfully submitted,

Date: August 29, 2007

By: _____
Ginger R. Dreger (Reg. No. 33,055)

HELLER EHRMAN LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

VIII. CLAIMS APPENDIX

Claims on Appeal

44. An isolated polypeptide comprising:

(a) the amino acid sequence of the polypeptide of SEQ ID NO: 96;

(b) the amino acid sequence of the polypeptide of SEQ ID NO: 96, lacking its associated signal peptide;

(c) the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 96; or

(d) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209397.

45. The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 96.

46. The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 96, lacking its associated signal peptide.

49. The isolated polypeptide of Claim 44 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209397.

50. A chimeric polypeptide comprising a polypeptide according to Claim 44 fused to a heterologous polypeptide.

51. The chimeric polypeptide of Claim 50, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.

52. The isolated polypeptide of Claim 44 comprising the amino acid sequence of the extracellular domain of the polypeptide of SEQ ID NO: 96.

IX. EVIDENCE APPENDIX

1. Declaration of Audrey Goddard, Ph.D. under 35 C.F.R. §1.132, with attached Exhibits A-G:

   A. Curriculum Vitae of Audrey D. Goddard, Ph.D.
   B. Higuchi, R. *et al.*, "Simultaneous amplification and detection of specific DNA sequences," *Biotechnology* 10:413-417 (1992).
   C. Livak, K.J., *et al.*, "Oligonucleotides with fluorescent dyes at opposite ends provide a quenched probe system useful for detecting PCR product and nucleic acid hybridization," *PCR Methods Appl.* 4:357-362 (1995).
   D. Heid, C.A. *et al.*, "Real time quantitative PCR," *Genome Res.* 6:986-994 (1996).
   E. Pennica, D. *et al.*, "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors," *Proc. Natl. Acad. Sci. USA* 95:14717-14722 (1998).
   F. Pitti, R.M. *et al.*, "Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer," *Nature* 396:699-703 (1998).
   G. Bieche, I. *et al.*, "Novel approach to quantitative polymerase chain reaction using real-time detection: Application to the detection of gene amplification in breast cancer," *Int. J. Cancer* 78:661-666 (1998).

2. Declaration of Avi Ashkenazi, Ph.D. under 35 C.F.R. §1.132, with attached Exhibit A (Curriculum Vitae).

3. Declaration of Paul Polakis, Ph.D. under 35 C.F.R. §1.132 (Polakis I).

4. Declaration of Paul Polakis, Ph.D. under 35 C.F.R. §1.132 (Polakis II).

5. Orntoft, T.F., *et al.* Molecular & Cellular Proteomics – 1:37-45 (2002).

6. Hyman, E., *et al.*, "Impact of DNA Amplification on Gene Expression Patterns in Breast Cancer," *Cancer Research* 62:6240-6245 (2002).

7. Pollack, J.R., *et al.*, "Microarray Analysis Reveals a Major Direct Role of DNA Copy Number Alteration in the Transcriptional Program of Human Breast Tumors," *Proc. Natl. Acad. Sci. USA* 99:12963-12968 (2002).

8. Hanna *et al.*, "HER-2/neu Breast Cancer Predictive Testing," Pathology Associates Medical Laboratories (1999).

9. Konopka *et al.*, "Variable Expression of the Translocated c-abl oncogene in Philadelphia-chromosome-positive B-lymphoid cell lines from chronic myelogenous leukemia patients" *Proc. Natl. Acad. Sci. USA* 83: 4049-52, (1986).

10. Sen *et al.* , Current Opinion in Oncology, 12: 82-88, (2000). (cited June 2, 2003)

11. Godbout, R., *et al.,* J. Biol. Chem. - 273(33):21161-8 (1998).

12. Bea, S., *et al.,* Cancer Res. - 61(6):2409-12 (2001).

13. Wildsmith *et al.*, "Gene Expression Analysis using Microarrays" Mol. Biol in Cellular Path. (2003) England: John Wiley & Sons, p 269-286.

14. Li *et al.*, 2006, Oncogene 25: 2628-2635.

Item 1 was submitted with Appellants' Response filed February 21, 2003, and was considered by the Examiner as indicated on June 2, 2003.

Items 2 and 8 were submitted with Appellants' Response filed May 21, 2004, and were considered by the Examiner as indicated on August 2, 2004.

Items 3, 5-7 were submitted November 3, 2004 and were made of record by the Examiner in the Office Action mailed January 13, 2005.

Item 4 was submitted with Appellants' Response filed March 30, 2006.

Items 1(E) and 9 were cited by the Examiner in the non-final rejection mailed January 21, 2004.

Item 10 was made of record by the Examiner in the Final Office Action mailed June 2, 2003.

Items 11-12 were submitted with Appellants' Response filed August 22, 2006, and were considered by the Examiner as indicated in the Final Office Action mailed November 1, 2006.

Items 13-14 were made of record by the Examiner in the Final Office Action mailed November 1, 2006.

X. RELATED PROCEEDINGS APPENDIX

None- no decision rendered by a Court or the Board in any related proceedings identified above.